

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020698

CHEMISTRY REVIEW(S)

NDA 19-797, amendments and supplements - NuLYTELY

CONSULTS:

None.

REMARKS/COMMENTS:

This amendment is the firm's response to an APPROVABLE action taken by the agency after the second Chemistry, Manufacturing, and Control review of this NDA. The Approvable letter was dated December 1, 1998. In the Approvable letter, six items of concern were raised which necessitated pre-approval consideration; three post-approval commitments were requested. All items of concern appear to have been adequately addressed in this amendment.

DMF [REDACTED] was found to be deficient [REDACTED] A deficiency letter was sent to the DMF holder. As of the date of this review, no response has been received. On February 11, 1999, a response to the deficiency letter was provided to this division in which the deficiencies were addressed satisfactorily.

APPEARS THIS WAY ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-698 CHEM.REVIEW #: 3 REVIEW DATE: 2/11/99

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Amendment	12/17/1998	12/18/1998	12/21/1998

NAME & ADDRESS OF APPLICANT: Braintree Laboratories
60 Columbian Street
P. O. Box 850929
Braintree, MA 02185-0929

FEB 16 1999

DRUG PRODUCT NAME

Proprietary: 851 Laxative
Nonproprietary/USAN: Polyethylene Glycol 3350, NF
Code Name/#:
Chem.Type/Ther.Class:

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOL.CATEGORY/INDICATION: Treatment of occasional constipation

DOSAGE FORM: Powder for reconstitution

STRENGTHS: N/A

ROUTE OF ADMINISTRATION: Oral

DISPENSED: Rx X OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Polyethylene Glycol

$H(OCH_2CH_2)_nOH$

Mol. Wt. = 3350

SUPPORTING DOCUMENTS:

IND
DMF

DMF
DMF
DMF
DMF

RELATED DOCUMENTS (if applicable):

BEST POSSIBLE COPY

NDA 19-797, amendments and supplements - NuLYTELY

CONSULTS:

None.

REMARKS/COMMENTS:

This amendment is the firm's response to an APPROVABLE action taken by the agency after the second Chemistry, Manufacturing, and Control review of this NDA. The Approvable letter was dated December 1, 1998. In the Approvable letter, six items of concern were raised which necessitated pre-approval consideration; three post-approval commitments were requested. All items of concern appear to have been adequately addressed in this amendment.

DMF [REDACTED] was found to be deficient [REDACTED]. A deficiency letter was sent to the DMF holder. As of the date of this review, no response has been received. On February 11, 1999, a response to the deficiency letter was provided to this division in which the deficiencies were addressed satisfactorily.

APPEARS THIS WAY ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

This application may be approved.

/S/

2/16/99

Raymond P. Frankewich, Ph.D.
Review Chemist, HFD-180

/S/

2/16/99

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:

Original NDA 20-698

HFD-180/Division File

DISTRICT FILE

HFD-181/CSO/AKacuba

HFD-820/EDuffy

HFD-180/RFrankewich/2-11-1999

R/D init: EDuffy/2/16/99

RF/rf/ F/T 2/11/99 c:\wordfiles\chem\nda\20698902.3rf

APPROVED

APPEARS THIS WAY ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

DEC - 1 1998

NDA #: 20-698CHEM.REVIEW #: 2REVIEW DATE: 12/1/98SUBMISSION TYPE

Amendment

DOCUMENT DATE

June 2, 1998

CDER DATE

June 3, 1998

ASSIGNED DATE

June 12, 1998

NAME & ADDRESS OF APPLICANT:

Braintree Laboratories
60 Columbian Street
P. O. Box 850929
Braintree, MA 02185-0929

DRUG PRODUCT NAMEProprietary:

851 Laxative

Nonproprietary/USAN:

Polyethylene Glycol 3350, NF

Code Name/#:Chem.Type/Ther.Class:ANDA Suitability Petition/DESI/Patent Status:PHARMACOL.CATEGORY/INDICATION:

Treatment of occasional
constipation

DOSAGE FORM:

Powder for reconstitution

STRENGTHS:

N/A

ROUTE OF ADMINISTRATION: OralDISPENSED:

Rx

X OTCCHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Polyethylene Glycol

 $H(OCH_2CH_2)_nOH$

Mol. Wt. = 3350

SUPPORTING DOCUMENTS:

IND

DMF

DMF

DMF

DMF

DMF

RELATED DOCUMENTS (if applicable):

CONSULTS:

None.

REMARKS/COMMENTS:

[REDACTED]

An Establishment Evaluation Request (EER) form was issued on April 1, 1996. The facilities to be evaluated were the ones listed in question C below, along with the facilities of the manufacturers of the PEG 3350 NF. The addresses of these facilities are:

[REDACTED]

It appears that all facilities have been classified as Acceptable by HFD-324, except for the [REDACTED] facility in [REDACTED]. An inspection was conducted in that facility on November 18, 1998. As of the date of the final draft of this review (December 1, 1998) no recommendation had been made regarding the compliance status of this facility.

[REDACTED]

Several labeling issues were raised in the first review of this NDA, but were not included in the deficiency letter (current policy is to discuss labeling concerns only after the

(application becomes Approvable). These deficiencies are provided as an addendum to this review.

Deficiencies that still exist with this application (including those concerning labeling) are listed in the Draft Deficiency section of this review. The first 12 deficiencies should be addressed pre-approval, while the last four may be addressed on a post-approval basis.

CONCLUSIONS & RECOMMENDATIONS:

This application is Approvable.

[REDACTED]

/S/

[REDACTED] 12/1/98
Raymond P. Frankewich, Ph.D.
Review Chemist, HFD-180

[REDACTED] 12/1/98
Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

APPEARS THIS WAY ON ORIGINAL

[REDACTED]

cc:

Original NDA 20-698
HFD-180/Division File
DISTRICT FILE
HFD-181/CSO/AKacuba
HFD-820/EDuffy
HFD-180/RFrankewich/11-9-1998
R/D init: EDuffy/
RF/rf/ F/T 12/1/98 c:\wordfiles\chem\nda\20698808.2rf

C APPROVABLE

McNeil

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

FEB 27 1997

NDA #: 20-698CHEM.REVIEW #: 1REVIEW DATE: 12/9/96SUBMISSION TYPE

ORIGINAL

DOCUMENT DATE

2/26/96

CDER DATE

2/28/96

ASSIGNED DATE

3/7/96

NAME & ADDRESS OF APPLICANT:

Braintree Laboratories

60 Columbian Street

P. O. Box 850929

Braintree, MA 02185-0929

DRUG PRODUCT NAMEProprietary:

851 Laxative

Nonproprietary/USAN:

Polyethylene Glycol 3350, NF

Code Name/#:Chem.Type/Ther.Class:ANDA Suitability Petition/DESI/Patent Status:PHARMACOL.CATEGORY/INDICATION:Treatment of occasional
constipationDOSAGE FORM: Powder for reconstitutionSTRENGTHS: N/AROUTE OF ADMINISTRATION: OralDISPENSED:

Rx

X OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Polyethylene Glycol

 $H(OCH_2CH_2)_nOH$

Mol. Wt. = 3350

SUPPORTING DOCUMENTS:

IND

DMF

DMF

DMF

DMF

DMF

RELATED DOCUMENTS (if applicable):

CONSULTS:

None (stability data is consulted to Biometrics only when at least 12 months of data has been received from the applicant, which is not the case with this particular submission).

REMARKS/COMMENTS:

An Establishment Evaluation Request (EER) form was issued on April 1, 1996. The facilities to be evaluated were the ones listed under Section 4 below (Manufacturer(s)), along with the facilities of the manufacturers of the PEG 3350 NF. The addresses of these facilities are:

As of December 9, 1996, no response has been received from HFD-324 regarding the compliance of these facilities, or any of those listed in Section 4 below.

The stability section of this NDA was not consulted to HFD-720. It was concluded that not enough information was provided to do a statistical analysis of the data.

APPEARS THIS WAY ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

This application is Not Approvable.

/S/

2/27/97

Raymond P. Frankewich, Ph.D.
Review Chemist, HFD-180

/S/

2/27/97

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

APPEARS THIS WAY ON ORIGINAL

cc:

Original NDA 20-698

HFD-180/Division File

DISTRICT FILE

HFD-181/CSO/MMcNeil

HFD-820/JGibbs

HFD-180/RFrankewich/12-9-1996

R/D init: EDuffy/2-27-97

RF/rf/dob F/T 2-27-97/WP: c:\wpfiles\chem\N\20698000.1RF

NOT APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020698

PHARMACOLOGY REVIEW(S)

McNeil

NDA 20,698

Review #1

Sponsor & Address: Braintree Laboratories, Inc.
Braintree, MA 02185-0929

SEP 20 1996

Reviewer: Ke Zhang, Ph.D.
Pharmacologist

Date of Submission: February 26, 1996

Date of HFD-180 Receipt: March 4, 1996

Date of Review: September 12, 1996

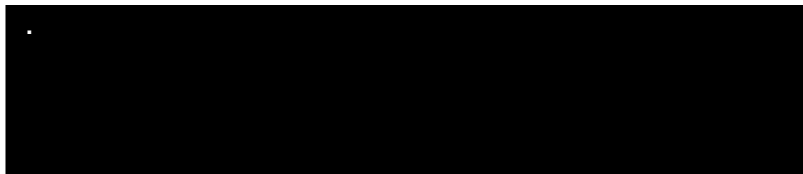
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

DRUG: 851 Laxative/polyethylene glycol 3350/PEG 3350,
Oral Powder, dissolved in 8 ounces of fluid

Molecular formula: $\text{HO}(\text{C}_2\text{H}_4\text{O})_n\text{C}_2\text{H}_4\text{OH}$, n: average 75 (68-84)
MW: Average 3350 (3000-3700)

CATEGORY: An osmotic agent for treatment of occasional constipation.

Related INDs and NDAs:



Marketing Indications and Dose: 851 Laxative is indicated for the treatment of occasional constipation. Subjects will be given 17 g or 0.34 g/kg (50 kg body weight assumed) of 851 Laxative (powder) orally. 851 Laxative should be dissolved in 8 ounces of fluid before ingested. The elderly patients will receive 12 g or 0.24 g/kg orally.

* see green tab for labeling recommendations

NDA 20,698

Page 2

PRECLINICAL STUDIES AND TESTING LABORATORIES:

Type of Study	Study #	Lot #	Lab
<u>Absorption, Distribution, Metabolism and Excretion (ADME)</u>			
rats (PEG 4000)	published reports		
<u>Acute Toxicity</u>			
Rats, rabbits, Guinea pigs (PEG 4000)	published reports		
<u>Subacute/Chronic Toxicity</u>			
90-day oral toxicity study in drinking water in rats (PEG 4000)	published report		
2-year oral toxicity study in rats (PEG 4000)	published report		
3-day oral toxicity study in dogs (PEG 3350)	2457-100	70232	1
1-year oral toxicity study in dogs (PEG 4000)	published report		
<u>Reproductive Toxicity</u>			
A Segment II study in rats (PEG 200)	published report		

The 3-day oral toxicity study in dogs (2457-100) was submitted in the present NDA and all other studies are published reports.

PHARMACOLOGY:

851 laxative is composed entirely of polyethylene glycol 3350 (PEG 3350). Sponsor did not conduct any pharmacological studies with 851 laxative in animals. However, PEG 3350 is an osmotic agent and major component in GoLYTELY and NuLYTELY (bowel cleansing agents) to evacuate the colon in preparation for colonoscopy. GoLYTELY and NuLYTELY are currently marketed in the U.S. and contain 236 g or 420 g PEG 3350, respectively, with various electrolytes. As an osmotic agent, PEG 3350 can increase the water content of the stool and produce a voluminous liquid stool when given orally. Therefore, it is expected to be therapeutically useful in the constipation patients.

NDA 20,698

Page 3

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION (ADME):

ABSORPTION: The absorption of PEGs was studied in the rats (J. Am. Pharmaceutical Association Sci. Ed. 36:152-157, 1947). In this study, rats were given orally 25% solutions of Carbowax 1000, 1540, 4000 and 6000. Carbowax 4000 contains 100% of PEG 3350. PEG 3350 and PEG 4000 have same molecular weights (3000-3700) and values of n (68-84, n = number of OCH_2CH_2 group). Therefore, Carbowax 4000 and PEG 4000 are referred to PEG 3350. The results indicated that there were no measurable absorption of the two high molecular weight PEGs (4000 and 6000) and a slight absorption (<2%) of the two low molecular weight PEGs (1000 and 1540) during a 5-hour period. A separate study indicated that 4.1% of an orally administered ^{14}C labelled PEG 4000 was recovered in the urine in rats (see below under excretion section), suggesting that the oral absorption of PEG 4000 can be as high as 4% in rats.

Metabolism: Sponsor stated there was no evidence of PEG 4000 being metabolized. However, no data were provided.

Excretion: The results of the studies on the excretion of PEG 4000 were summarized in the pharmacology review of NDA 19,797 dated April 28, 1989 and these were reproduced below.

Excretion: In the rats, orally administered ^{14}C -labeled PEG 4000 resulted in 7-day cumulative recovery of 86%, of which 81.9% appeared in the feces, 4.1% in the urine, and none in the expired CO_2 . The mean cumulative recovery following iv injection was 81%, of which 20% was in the feces, 61% in the urine, and none in the expired CO_2 . Virtually no drug was found in the carcass (Carpenter et al., Toxicology and Applied Pharmacology 18: 35-40, 1971, page 193 of submission, volume 2.2; only the rat data were extracted from the report). In the humans, following intravenous injection, it is rapidly excreted unchanged via the urine within 24 hours. Orally administered PEG-3350 from PEG-ELS is excreted via feces in a voluminous liquid stool with no effects on the colonic histology. The $t_{1/2}$ of PEG-3350 from PEG-ELS in humans is about 7 hours. Further, PEG-3350 is not fermented into hydrogen or methane by the colonic microflora.

In summary, pharmacokinetic profile of PEG 4000 was characterized in rats. The results indicate that there was minimal oral absorption of PEG 4000 (0-4%) in rats and following i.v. injection PEG 4000 was excreted via urine (75% of total recovered radioactivity) and feces (25%). In humans, the oral absorption of PEG 3350 was minimal (~0.2%) and PEG 3350 was quickly excreted via urine when given intravenously. The half life of PEG 3350 was ~7 hours in human. PEG 3350 was not fermented into hydrogen or methane by the colonic microflora in human feces.

NDA 20,698

Page 4

TOXICITY:

ACUTE TOXICITY:

The acute toxicity studies with Carbowax 4000 submitted in this submission were previously reviewed in NDA 19,797 on April 28, 1989. This review is reproduced below.

Acute toxicity of PEG-3350 in various animal species is summarized in Table 1.

Table 1
Acute Toxicity of Various PEGs*

Compound Tested	Species/ sex	LD ₅₀ g/kg	Symptoms/Effects
<u>Oral Route</u>			
Carbowax 4000, <u>po</u> (PEG-3500)	Rat, M	> 50	No clear effects were described, however, it was stated that rats that died with large doses of PEG, were found to have renal lesions and cloudy swelling of the livers.
Carbowax 4000, <u>po</u>	Rat, M	> 59	Same as above.
Carbowax 4000**, <u>po</u>	Rat, M	> 50	Same comments as above.
Carbowax 4000, <u>po</u>	Rabbit, M	> 76	No animals died; blood urea was elevated in some animals given a single 50 g/kg dose; there was no renal pathology unlike seen in the rats.
Carbowax 4000, <u>po</u>	Guinea pig, M&F	> 50	No data were provided.
Carbowax 4000, <u>po</u>	Guinea pig, M&F	> 50.9 (39.1-66.1)	No data were provided.
<u>Intravenous Route</u>			
Carbowax 4000, <u>iv</u> 20% solution	Rat, sex unknown	7.5 g/kg	Deaths probably from thrombosis, because clumping of cellular elements was seen in in-vitro tests with 10% solution.
Carbowax 4000, <u>iv</u> infusion	2 Male Rabbits	> 10 g/kg	No deaths; one rabbit showed cloudy swelling of the renal tubules.

*=Extracted from 'The Toxicology of the Polyethylene Glycols', Smyth et al., J. Am. Pharm. Assn. 39: 349-354, 1950 (pages 269-274 of submission, volume 2.2). The Wistar rats were used in the tests prior to 1945, and later Sherman white rats, the rabbits were of New Zealand strain, and the strain of the guinea pigs was not mentioned. Further, it was stated that too few animals (exact numbers not given) were used in the tests. However, it should be noted that these studies were conducted prior to GLP regulations.

**=specially purified sample was employed.

NDA 20,698

Page 5

Minimal lethal dose was not given in the published report (J. Am. Pharm. Association 39:349-354, 1950).

SUBACUTE/CHRONIC TOXICITY:

RATS:

A two-year oral (in diet) toxicity study with PEG 4000 in rats
(J. American Pharmaceutical Association, XLIV (1):27-30, 1955)

Methods: To determine the chronic toxicity of PEG 4000 in rats, Wistar rats (20/sex/group) were treated with PEG 4000 at 0, 0.5, 1, 2, 4 and 8% (approximately 0, 0.313, 0.625, 1.25, 2.5 and 5 g/kg/day) in diet. Following parameters were monitored: mortality, food consumption, body weight, hematology and organ weights (liver and kidney at 1 and 2 years). Gross and histopathological examinations were conducted on the rats died before termination and at one year after treatment. The histopathological examination was conducted on adrenal, heart, small intestine, kidney, liver, lung, pancreas, spleen and testis. After 2 years, the survivors were sacrificed and liver and kidney weights were determined.

Results: There were no treatment related deaths in this study. The authors stated that the rats treated with 8% PEG 4000 "grew somewhat less" than control rats. This was the only treatment related change in this study. In conclusion, based on the available data, the no effect dose was identified at 4% and the target organ of toxicity was not identified.

DOGS:

There was a 3-day oral toxicity study using PEG-3350 in dogs submitted in this submission and this study was previously reviewed in NDA 19,797 on April 28, 1989. This review is reproduced below.

3-Day Oral Toxicity Study in the Dogs
(Project # [REDACTED] 2457-100)

Conducting Lab: [REDACTED]

Dates of Conduct: Initiated April 6, 1987, completed April 9, 1987

GLP Statement: In compliance with FDA's GLPs.

MATERIALS AND METHODS

Chemical: PEG 3350, Vet-Prep; lot # 70232 in distilled water.
Animals: Beagle dogs, 6-8 kg males, and 4-6 kg females; 3/sex/group
Doses: 0 (control vehicle) and 26.4 ml/kg/10 hours (=15.8 g/kg/d).

NDA 20,698

Page 6

Methods: The dogs were given the test substance or control vehicle by gavage once every hour for 10 hours daily for 3 days. The animals were observed daily for morbidity; the body weights, food and water consumption were recorded initially and daily for 3 days. Hematology, clinical chemistry and ophthalmology were also recorded. However, the frequency of blood collection was not mentioned. At termination, all the animals were sacrificed and necropsied. The tissues/organs were weighed and examined macro- and microscopically.

Results: There were no deaths. All drug-treated dogs had soft stools and diarrhea during the treatment.

There were no significant drug-related changes in body weights, ophthalmic examinations, food consumption, clinical chemistry (including SGOT, SGPT, total bilirubin, BUN, serum creatinine and serum osmolality), hematology (including platelets), organ weights (except kidneys, see below).

Organ weights: The absolute kidney weights in the treated male dogs were higher ($p < 0.05$) than the controls (42.3 v/s 47.1 g) but not in the females (36.4 g in the treated v/s 35.4 g in the control dogs). The relative weights did not seem to differ significantly (males 0.60 v/s 0.70, and females 0.68 v/s 0.73).

Histopathology: There were no remarkable histological changes in any organ.

In summary, PEG-3350 tested at 15.8 g/kg/d for 3 days produced no significant toxicity in the beagle dogs except soft stools and diarrhea.

A 1-year oral (in diet) toxicity study of PEG 4000 in dogs
(J. American Pharmaceutical Association, XLIV (1):27-30, 1955)

Methods: To study the chronic toxicity of PEG 4000, dogs (4/group) were given PEG 4000 in diet at 0 and 2% (~0.5 g/kg/day) for one year. One dog also received 8% PEG 4000 in diet (~2 g/kg/day) for one year. Initial and terminal body weights were determined. The following parameters at termination were determined: liver and kidney weights, red blood cell counts, plasma hemoglobin level, prothrombin time, serum urea nitrogen, alkaline serum phosphatase and plasma cholinesterase activities and bromsulfalein retention times. All dogs were necropsied after one year and histopathological examination was conducted. The following organs were histopathologically examined: adrenal, bladder, heart, kidney, liver, lung, pancreas, small intestine, stomach, spleen, thyroid and testis or ovary.

NDA 20,698

Page 7

Results: There were no deaths in this study. The results revealed no significant treatment related changes in all parameters including the histopathological examinations. There was a slight decrease of terminal body weight in the dogs treated with PEG 4000 at 2% (-0.58 kg) as compared to the control (+0.28 kg). This is not considered treatment related since the terminal body weight in the dog treated with PEG 4000 at 8% was actually increased by 0.52 kg. In conclusion, based on the available data, PEG 4000 did not produce any toxicity at the doses tested (2% and 8% in diet).

REPRODUCTIVE TOXICITY:

There were no reproductive toxicity studies conducted with PEG 3350. The following study conducted with PEG 200 is reviewed below.

A Segment II teratologic study following oral administration of PEG 200 in rats

Methods: This is an abstract provided by sponsor in this submission. To investigate the teratogenic potentials of PEG 200, rats were given oral doses of PEG 200 at 0, 1 and 10 g/kg/day during gestation days 6 to 15. The authors did not specify the method of administration (oral gavage or in diet). The litter size, body weights, gross appearance, skeletal and visceral status of the fetuses were evaluated.

Results: No data were provided in this abstract. However, authors stated that PEG 200 was not teratogenic.

LABELLING:

The labelling is according to 21 CFR, Subpart B. The following revision in the labelling is recommended:

Sponsor's Version:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic and reproductive studies in animals have not been performed.

Evaluation: Genetic toxicity studies have not been performed with laxative 851.

NDA 20,698
Page 8

Suggested Version:

Long term carcinogenicity studies, genetic toxicity studies and reproductive toxicity studies in animals have not been performed with laxative 851. (851 laxative?)

SUMMARY AND EVALUATION:

Polyethylene glycol 3350 (PEG 3350) is a nonabsorbable osmotic agent and used in GoLYTELY and NuLYTELY (bowel cleansing agents) to evacuate the colon in preparation for colonoscopy. GoLYTELY and NuLYTELY are currently marketed in the U.S. and contain 236 g or 420 g PEG 3350, respectively, with various electrolytes. 851 laxative is composed entirely of PEG 3350. As an osmotic agent, when given orally, PEG 3350 can increase the water content of the stool, produce a voluminous liquid stool and increase the bowel movement and thus is expected to be therapeutically useful in the constipation patients.

In the present NDA, sponsor is asking for approval to market 851 Laxative for the treatment of occasional constipation. Patients will be given 17 g or 0.34 g/kg (50 kg body weight assumed) of 851 Laxative (powder) orally. 851 Laxative should be dissolved in 8 ounces of fluid before ingested. The elderly patients will receive 12 g or 0.24 g/kg orally. In support of this NDA, the following preclinical studies either were submitted in this submission or are published reports: absorption, distribution, metabolism and excretion (ADME) studies in rats, oral toxicity studies: acute toxicity studies in mice, rats and guinea pigs, a 90-day toxicity study in drinking water in rats, a 2-year oral toxicity study in diet in rats, a 3-day toxicity study by oral gavage in dogs and a 1-year toxicity study in diet in dogs, oral reproductive toxicity study: a Segment II teratological study in rats. Some of these studies were conducted with Carbowax 4000. Carbowax 4000 contains 100% of PEG 3350. PEG 3350 and PEG 4000 have same molecular weights (3000-3700) and values of n (68-84, n = number of OCH_2CH_2 group). Therefore, Carbowax 4000 and PEG 4000 are referred to PEG 3350.

The oral absorption of PEG 4000 was ~0-4% in rats. PEG 4000 was excreted via urine (75% of total recovered radioactivity) and feces (25%) following i.v. injection. There was no evidence of PEG 4000 being metabolized. The oral absorption of PEG 3350 in human was also very limited (~0.2%) and PEG 3350 was quickly excreted via urine when given intravenously. The half life of PEG 3350 was ~7 hours in human. PEG 3350 was not fermented into hydrogen or methane by the colonic microflora in human feces.

NDA 20,698

Page 9

In the acute toxicity studies in rats, rabbits and guinea pigs, no clinical signs of toxicity were provided. LD₅₀ and the cause of death were not clearly identified. In the dead rats, renal lesions and cloudy swelling of the livers were seen. Minimal lethal dose was not identified.

In the summary of 90-day oral (in drinking water) toxicity study in rats (J. Am. Pharm. Association 39:349-354, 1950), following information were provided: cloudy swelling of the kidneys at 0.08 g/kg/day or higher and testicular degeneration at 0.23 g/kg/day or higher. No effect dose was identified at 0.04 g/kg/day.

In the 2-year oral toxicity study in rats, rats were given PEG 4000 in diet at 0, 0.313, 0.625, 1.25, 2.5 and 5 g/kg/day for 2 years. The only treatment related changes were retarded body weight gain at 5 g/kg/day. The no effect dose was identified at 2.5 g/kg/day and the target organ of toxicity was not identified.

In the 3-day oral toxicity study in dogs, dogs were given PEG 3350 at 0 and 15.8 g/kg/day by oral gavage for 3 days. All treated dogs had soft stools and diarrhea.

In the 1-year oral toxicity study in dogs, dogs were given PEG 4000 in diet at 0, 0.5 and 2 g/kg/day for one year. Based on the available data, PEG 4000 did not produce any toxicity at the doses tested (0.5 and 2 g/kg/day).

In the Segment II teratological study in rats, PEG 200 was given to rats during gestation days 6 to 15. No data were provided in this report but the authors stated that PEG 200 was not teratogenic.

The mutagenic potential of PEG 3350 was not tested.

The labelling should be revised as suggested in the labelling portion.

No specific organs of toxicity can be identified clearly.

NDA 20,698

Page 10

RECOMMENDATION:

1. From a preclinical standpoint, this NDA is approvable. AP & AE?
2. Sponsor should be asked to revise the labelling as recommended.

/S/

Ke Zhang, Ph.D.

9/12/96

NDA

HFD-180

HFD-181/CSO

HFD-180/Dr. Choudary

HFD-180/Dr. Fredd

HFD-180/Dr. Zhang

HFD-345/Dr. Viswanathan

HFD-102/Assistant Director (Pharmacology)

/S/

9/20/96

R/D Init.: J. Choudary 8/12/96

KZ/hw/8/20/96

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APPEARS THIS WAY ON ORIGINAL